Convenient metal-free *ipso*-nitration of arylboronic acids using nitric acid and trifluoroacetic acid

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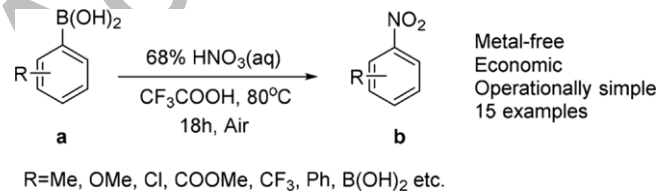
Abstract

A feasible protocol for the direct *ipso*-nitration of arylboronic acids using trifluoroacetic acid and nitric acid as nitration reagent has been developed. Various aromatic nitro compounds are produced in moderate to good yields under the metal-free condition. The method is operationally simple, regioselective, and might have potential application in industry.

GRAPHICAL ABSTRACT



KEYWORDS: Metal-free, *ipso*-Nitration, Arylboronic acids, Nitroarenes

INTRODUCTION

Nitroarenes are important building blocks for the chemical industry and organic synthesis.[1–9] Widespread applications have also been found in pharmaceuticals, dyes and materials.[10–12] The electrophilic *ipso*-nitration of arenes is one of the most classic methods, which involves the use of either the mixture of nitric and sulfuric acid, or dinitrogen pentoxide.[2] However, the problem of regioselectivity and functional group tolerance can not be solved under such drastic reaction conditions. Therefore, the development of mild and operationally simple methods for regioselective nitration is of great significance in organic synthesis.

In 2000, Prakash and Olah *et al.* firstly reported the *ipso*-nitration of arylboronic acids by using NH_4NO_3 and $(CF_3CO)_2O$ as nitration reagent.[13] In 2004, another nitration protocol was disclosed by applying $AgNO_3$ and TMSCl as selective and efficient nitrating agents.[14] Due to the requirements of economic and easy operation, more and more attentions had been paid in the exploring novel methods for the *ipso*-nitration of arylboronic acids. Recently, several good methods have been reported, such as *tert*-butyl nitrite/dioxane, $NaNO_2$, Cu_2O/NH_3-H_2O, $Bi(NO_3)_3/K_2S_2O_8$/toluene, $Bi(NO_3)_3$/toluene, TMSCl/$NaNO_2$/DCM and others.[15–20] However, some methods need to use large amount of metal salts and harsh reaction conditions, limiting their applications in industry. Here we proposed an economic, operationally simple, regioselective protocol for the synthesis of aromatic nitro compounds by direct *ipso*-nitration of arylboronic acids using trifluoroacetic acid and commercial available 68% nitric acid aqueous solution.

RESULTS AND DISCUSSION

Initially, benzeneboronic acid **1a** was selected as the model substrate and the reaction conditions were systematically evaluated (Table 1). The reaction was firstly carried out in AcOH (1.0 mL) and 92.6 mg of 68% nitric acid aqueous solution (HNO_3 1.0 mmol) at 80 ^oC under N_2 atmosphere without metal catalyst. After 24 hours, the reaction was stopped and the anticipated product **1b** was isolated in 10% yield after flash chromatography (Table 1, entry 1). Then 92.6 mg of 68% nitric acid aqueous solution (HNO_3 1.0 mmol) was used to repeat the reaction and trace **1b** was detected (Table 1, entry 2). When AcOH was replaced by H_3PO_4, the result show that only trace **1b** was found (Table 1, entry 3). When CF_3COOH was used to run the reaction, delivering the target product in 31% yield (Table 1, entry 4). The reaction was also surveyed at 70 and 85 ^oC, but the reaction worked at 80 ^oC provided the best yield (Table 1, entries 5 and 9). To our delight, When CF_3COOH and 68% nitric acid aqueous solution were used to run the reaction under air atmosphere, the yield rose up to 76% (Table 1, entry 6). From the experiments we can conclude that the air has the effect on deborylation or oxidization in this reaction.[8] Then we increased the amount of nitric acid to 3.0 eq and reduced the reaction time to 18 h, the yields were not changed (Table 1, entries 7 and 8). From reaction entries 9 and 10, we can conclude that the reaction temperature, air and trifluoroacetic acid are important to this reaction. Only using nitric acid aqueous solution in the reaction, we got **1b** in 12% yield (Table 1, entry 11). Obviously, entry **8** represents the best condition. Furthermore, we also used 20g benzeneboronic acid **1a** to repeat the reaction, and obtained the product **1b** in 72% yield (Table 1, entry 12).

After the reaction condition was optimized, the scope was explored with various arylboronic acids **a**. The results are listed in Table 2. The substituted arylboronic acids bearing both electron-donating groups (*o*-Me, *m*-Me, *p*-Me, *o*-OMe, *p*-OMe) and electron-withdrawing groups (*o*-Cl, *m*-Cl, *p*-Cl, *m*-COOMe, *p*-COOMe and *m*-CF_3) were able to proceed the reaction and gave the products in moderate to excellent yields (Table 2, entries 2-12). The reaction seemed sensitive to the electronic effect and sterical hindrance on the arylboronic acids **a**. The reaction yields of *o*-tolylboronic acid **2a** and *o*-chlorophenylboronic acid **5a** are relatively lower than *p*-tolylboronic acid **4a** and *p*-chlorophenylboronic acid **6a** (Table 2, entries 2, 4, 5 and 6). The *m*-substituted arylboronic acids have much lower yields due to the electronic effect (Table 2, entries 3, 10 and 11).[21] Because of the electron-donating group -OMe, the main product of 4-methoxyphenylboronic acid **7a** is 1-methoxy-2,4-dinitrobenzene **7b** in high yield (Table 2, entry 7), the reaction of 2-methoxyphenylboronic acid **8a** got a mixture (Table 2, entry 8). 3-(Methoxycarbonyl)phenylboronic acid **9a** and 4-(methoxycarbonyl)phenylboronic acid **10a** were also suitable for this reaction and the corresponding hydrolysis products were detected (Table 2, entries 10 and 11). The yield of 4-(trifluoromethyl)phenylboronic acid **12a** with strong electron-withdrawing functional group only gave 40% yield (Table 2, entry 12). 1,4-Phenylenediboronic acid **13a** reacted smoothly and 1,4-dinitrobenzene **13b** was got (Table 2, entry 13). Interestingly, the reaction of biphenyl-4-ylboronic acid **14a** got the product 2,4'-dinitrobiphenyl **14b** (Table 2, entry 14). However, 3,5-difluorophenylboronic acid **15a** did not undergo nitration under the reaction condition (Table 2, entry 15). From the above results we could conclude that the nitration reagent of trifluoroacetic acid and

nitric acid is efficient and the corresponding products are got in moderate to excellent yields under the metal-free condition.

EXPERIMENTAL

Sample procedure for the *ipso*-nitration of arylboronic acids **2a**: An round bottle flask was charged with a magnetic stir bar, arylboronic acid **2a** (0.5 mmol), trifluroacetic acid 1.0 mL and 92.6 mg of 68% nitric acid aqueous solution (HNO_3 1.0 mmol), then the mixture reacted at 80 ^oC under air atmosphere for 18h. The reaction was stopped and cooled to room temperature. The reaction mixture was directly passed through Celite and rinsed with an additional 30 mL of AcOEt. The combined filtrate was washed by 1mol/L $NaHCO_3$, H_2O, then dried by $NaSO_4$. The dried AcOEt solution was concentrated and purified by column chromatography to give the product **2b** (48 mg, 70%) as yellow oil. ^1H NMR (400MHz, $CDCl_3$/TMS): δ 2.59 (s, 3H), δ 7.38 (t, J = 8.0 Hz, 1H), δ 7.49 (d, J = 8.0 Hz, 1H), δ 8.01 (d, J = 8.0 Hz, 1H), δ 8.02 (s, 1H). ^{13}C NMR (100MHz, $CDCl_3$/TMS): 20.5, 124.7, 127.0, 132.9, 133.1, 133.7, 149.4. MS (EI) *m/z* (M^+) 137.0.

CONCLUSION

In summary, a metal-free methodology for the *ipso*-nitration of various arylboronic acids has been established. Notably, using inexpensive trifluoroacetic acid and nitric acid as nitration reagent, different nitroarenes are produced in moderate to good yields. The method is operationally simple, regioselective, and might have potential application in industry.

ACKNOWLEDGMENT

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Supporting Information: Full experimental detail, ^{1}H and ^{13}C NMR spectra. This material can be found *via* the "Supplementary Content" section of this article's webpage.

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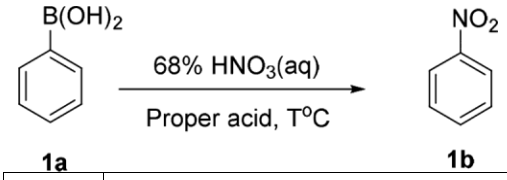
Table 1. Optimization of the reaction conditions[a]



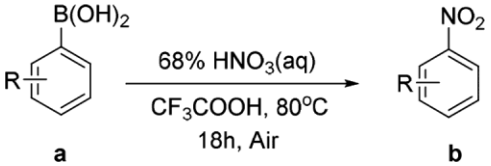
Entry	Catalyst	T(°C)	Time(h)	Yield(%)[b]
1	CH_3COOH/HNO_3(2.0 eq)/N_2	80	24	10
2	HNO_3(2.0 eq)/N_2	80	24	TRACE
3	H_3PO_4/HNO_3(2.0 eq)/N_2	80	24	TRACE
4	CF_3COOH/HNO_3(2.0 eq)/N_2	80	24	31
5	CF_3COOH/HNO_3(2.0 eq)/N_2	85	24	30
6	CF_3COOH/HNO_3(2.0 eq)/Air	80	24	76
7	CF_3COOH/HNO_3(3.0 eq)/Air	80	24	75
8	CF_3COOH/HNO_3(2.0 eq)/Air	80	18	76
9	CF_3COOH/HNO_3(2.0 eq)/Air	70	18	60
10	CH_3COOH/HNO_3(2.0 eq)/Air	80	24	15
11	HNO_3(2.0 eq)/Air	80	18	12
12	CF_3COOH/HNO_3(2.0 eq)/Air	80	18	72[c]

[a]Reaction conditions: benzeneboronic acid (0.5 mmol), proper acid 1.0 mL and 68% nitric acid aqueous solution (HNO_3 1.0 mmol) under N_2 or air atmosphere.

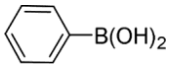
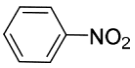
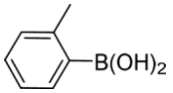
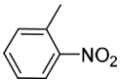
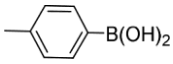
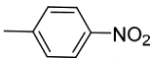
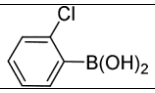
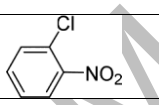
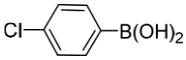
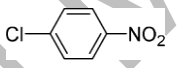
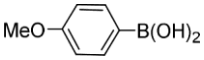
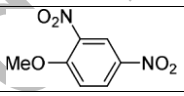
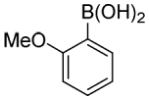
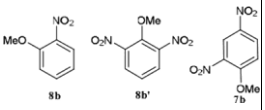
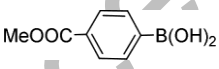
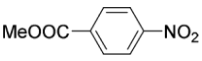
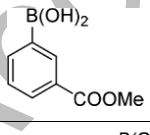
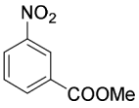
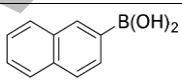
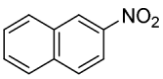
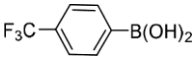
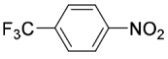
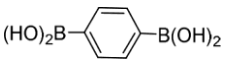
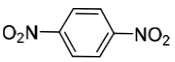
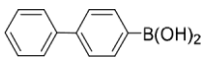
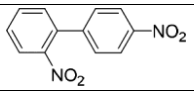
[b] Isolated yield after flash chromatography based on benzeneboronic acid.

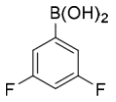
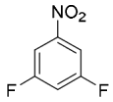
[c]20g of benzeneboronic acid **1a** was used.

Table 2. Nitration of different arylboronic acids[a]



a b

Entry	Arylboronic acids		Products		Yield(%)[b]
1		**1a**		**1b**	76
2		**2a**		**2b**	70
3		**3a**		**3b**	52
4		**4a**		**4b**	84
5		**5a**		**5b**	61
6		**6a**		**6b**	95
7		**7a**		**7b**	91
8		**8a**			8b/8b'/7b: 8/20/47
9		**9a**		**9b**	43[c]
10		**10a**		**10b**	55[d]
11		**11a**		**11b**	41
12		**12a**		**12b**	40
13		**13a**		**13b**	63
14		**14a**		**14b**	46

15		**15a**		**15b**	/[e]

[a] Reaction conditions: arylboronic acids (0.5 mmol), trifluroacetic acid 1.0 mL and 68% nitric acid aqueous solution (HNO_3 1.0 mmol) at 80 ^oC under air atmosphere for 18h.

[b] Isolated yield after flash chromatography based on arylboronic acids.

[c] Reacted for 12h and 18% 4-nitrobenzoic acid was got.

[d] Reacted for 12h and 10% 3-nitrobenzoic acid was got.

[e] No product was detected